Remarks

Claim 65 has been amended to incorporate the limitations of claim 66. Claims 66, 94 and 121 has been cancelled. Claims 122, 123 and 124 are new. Support for claim 122 can be found, e.g., on page 28, line 9 (para. [213] of US Patent Pub. 20070178469), support for claim 123 can be found, e.g., on page 12, line 50 (para. [0090]) and support for claim 124 can be found in original claims 1 and 3 and page 6, lines 42 to page 7, line 17 (paras. [0039], [0040], [0043] and [0044] of the publication). Claim 106 has been brought into independent form to incorporate the limitations of claim 105, which had been identified as withdrawn generic claim but is still part of the elected group of claims (see claim 106, whose limitations claim 105 now contains). Claims 15-17, 23, 24, 26, 28, 34, 42-45, 48, 49, 51, 55, 62-64, 69, 92-93, 95-100, 109 and 110 are withdrawn from consideration as being directed to a non-elected invention.

Claims 1-14, 18-22, 25, 27, 29-33, 35-41, 46-47, 50, 52-54 and 56-61 have previously been canceled without prejudice. Claims 72, 80, 82, 90, 103 and 105 continued to be identified as withdrawn generic claims, with the provisionally elected invention now being covered by claims 106, 107, 116-120 and 124.

Accordingly claims 65-68, 71, 74-79, 81, 83-89, 91, 101, 102, 106, 107, 108, 111-120 and 122 to 124 are presented for consideration.

Election/Restriction

The Office's acknowledged in the restriction requirement of June 18, 2010, that, upon indication of the allowability of the generic claim(s), the restriction requirement between the sequences shall be withdrawn and any claim(s) depending from or otherwise requiring all limitations of the allowable linking claim(s) will be rejoined.

However, to further the prosecution of the present application, applicants have further amended the subset of generic claims that is directed at **SEQ ID NOs: 24-27**, namely by further specifying the following characteristics of the DNA sequence:

> "having a melting temperature of between 55 and 75° and a DNA bending value of 4 radial degrees, wherein said bent DNA element comprises at least five contiguous AT or TA nucleotides and wherein said binding protein is a transcription factor"

See claims 72, 80, 82, 90, and in modified form, claim 103.

Due to the amendment of claim 65, the bent DNA element of these claims is also limited to:

> "comprising at least 33% of the dinucleotide TA and/or at least 33% of the dinucleotide AT on a stretch of 100 contiguous base pairs"

These characteristics have also been introduced, where required, into claims directed towards SEQ ID NO: 25, e.g., 106. Support for these amendments can be found in the original claims and e.g. on page 12 of the specification, starting at line 6, in particular line 49, page 6, lines 45 to 47 and page 11, starting at line 5.

The Office, citing MPEP 1850 (which discusses PCT Rule 13.2), acknowledged that SEQ ID NOs: 24-27 have a common property or activity (A), but expressed the opinion that these sequences lacked a significant structural element that is shared by all of the alternatives (B)(1).

The Office expressed the opinion that the common structure of the sequences, namely 10% TA or 12% AT on a stretch of 100 contiguous base pairs and the fact that they contain a binding site for DNA binding protein does not make a contribution over the prior art as evidenced by US Patent 6,245,974 to Michalowski et al. (e.g. SEQ ID NO. 5, first 100 nucleotides, which are said to contain more than 10 TA dinucleotides).

Applicants have amended claims 72, 80, 82, 90, 103 and 105 to specifically refer to a TA and AT content of above 33% and the presence of a specific DNA bending values, not present in Michalowski et at.

In view of these amendments which remove the basis for the Office's restrction requirement, applicants respectfully requests further reconsideration of the restriction requirement between SEQ ID NOs: 24, 25, 26 and 27.

The Office's attention is directed to independent claims 103 which contains characterizing features apparently not considered by the Office.

SPECIFICATION

On page 4 of the Office Action, the Office continued to reject the usage of the trademark "SMAR Scan®" and requested that the mark should be capitalized in accordance with MPEP 608.01(v).

In response, applicants have amended the specification as suggested.

CLAIM OBJECTIONS

Starting on page 4, the Office objected to claims 106 and 107 and 121 because they depend on non-elected claim 105. In response, claim 106 has been brought into independent form to incorporate the limitations of claim 105.

35 USC 112, FIRST PARAGRAPH REJECTION

Starting on page 5, the Office rejected claims 65-91, 101-104, 108 and 112-121 under 35 U.S.C., first paragraph, as failing to comply with the written description requirement.

In particular, the Office expressed the opinion that the invention encompasses a large genus of nucleic acid sequences of varying length (longer or equal to 100 base pairs) which have at least 10% of the TA and/or 12% AT on a stretch of 100 base pairs, regardless whether they possess protein production increasing activity greater than that of cLysMAR in any setting (in vitro, in vivo, or in transgenic organisms).

The Office acknowledged that the specification discloses the identification of MAR sequences which may increase protein expression in CHO cells through bioinformatics computational algorithms as well as four selected sequences that show the claimed protein production increasing activity.

The Office also acknowledges that possession should be scrutinized in accordance with the standards set forth in *Lockwood v American Airlines Inc.,* 107 F.3d, 1565, 41 USPQ2d 1961 (Fed. Cir. 1997).

However, the Office expressed the opinion that the specification does not disclose whether any sequence with 10% TA and/or 12% AT on a stretch of 100 base pairs and a DNA binding site would have protein producing increasing activity in any setting (in vitro, in vivo or in transgenic organism).

In the following, the Office refers to the background section and the prior art on record to support that the prior art at the time of filing does not make up for perceived deficiencies of the specification.

Applicants agree with the Office analysis in so far as that the prior art and the background section of the present application support that the invention makes a contribution over the prior art.

However, applicants disagree with the Office's assertions that (1) the specification

fails to describe sufficient identifying characteristics of the claimed genus of nucleic acids that have the recited structure and function and (2) the present disclosure fails to describe a representative number of species of nucleic acids that have the recited structure and can increase protein production in CHO cells greater than cLysMAR. Applicants also note the present amendments to independent claims 65 and 101.

Applicants respectfully submit that, while the method is not under prosecution, the identifying characteristic that the Office considers missing become apparent from a review of the method with which the four sequences the Office refers to were found.

However, prior to pointing out the identifying characteristics, applicants would like to note that it is well established that a description of a "representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" (MPEP §2163 IIA 3(a)).

Additionally, applicants would like to emphasize that *Lockwood*, as cited by the Office, specifically sanctions identifying characteristics other than primary sequences as sufficient to show possession. Those include, e.g., unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity and may be sufficient to show possession of the claimed invention to one of skill in the art. See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

As discussed above, the present description of the method describes the identifying characteristics.

A genome data set is first screened to identify bent DNA elements, as regions corresponding to the highest bent value, the highest "major groove depth", the highest "minor groove width", and the lowest "melting temperatures" (p. 7, lines 22-32; example 6, p. 27 and 28). Secondly, the so selected sequences are scanned for binding sites for regulatory proteins. For the selection of "super MARs" only sequences related to transcription factors with more than 20 hits were further considered (p. 29, line 10 and following).

Thus, identifying characteristics include "bending value", "major groove depth", "minor groove width", "melting temperatures" and binding sites. These identifying characteristics are described throughout the specification: e.g., page 12, starting at line 40 provides, e.g., specific DNA bending values (3.8 to 4.4 etc.), major groove depth values, minor groove width values, melting temperatures and transcription factor binding sites. The examples provide further specific values. Thus, the parameters for which the method of the present

invention selects provides exactly the identifying characteristics that the Offices considers to be lacking. The parameters set forth in the specification are not unlike DNA sequence information that provides identifying characteristics for sequences which owe their function to their primary sequence. For DNA elements whose function is largely based on structural features rather than their primary sequence, the discussed identifying characteristics indicate to the person skilled in the art possession of the claimed invention.
The specific default cut-off values of SMAR SCAN for, e.g., major groove depth and minor grove width, DNA bending values and melting temperatures are provided and the latter have been integrated into claims 72, 80, 82, 80, 103 and 105 (as well as higher AT/TA values (see claim 65 and 101 from which these claim depend), a specific DNA bending value and identifying the binding protein as transcription factor to further clarify the degree of variation that the reference to “a sequence complementary thereof, and a fragment or variant thereof” allows for).

The Office expressed the opinion that the present disclosure fails to describe a representative number of species of nucleic acids that have the recited structure and can increase protein production in CHO cells greater than cLysMAR.

The Office is, in this context, directed at claims 101 and following, which have been further amended and combine identifying structural characteristics with specific dinucleotide TA and/or dinucleotide AT percentiles. Support for these amendments can be found, e.g., on page 12, starting on line 6 to page 14, line 47 (paras. [0085]-[0108] of the publication).

As the Office noted what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. A satisfactory disclosure of a "representative number" depends on “whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed” (MPEP §2163 II A 3(b)).
As the Office noted, the specification provides the %AT/TA percentiles of cLysMAR in Table 6. The specification also quantifies cLysMAR’s capacity to enhance gene expression as well as that of four further sequences, e.g. in Figure 19. The specification further discloses that, with the tool thoroughly described in the specification, using the default settings and a bending value of more than 4 radial degree, only a small percentile of the genome was determined to be occupied

by potential "super" S/MARs (1757), which represents 0.35% of the genome (page 28, starting on line 3).

Applicants note that the specification describes that the four MAR elements were randomly selected, with three stemming from chromosome 1 (which is disclosed to contain 85 predicted S/MARs) and one from chromosome X (which is disclosed to contain 170 predicted S/MARs). All four of these MARs turned out to be "super" MARs (Example 16, page 40, starting at line 35; and Table 2 on page 28).

Applicants submit that the sufficiency of the written description requirements of a structure that is made of DNA but whose function is primarily determined by structural features rather than by the DNA's primary sequence, has to be determined based on the disclosure of these structural features, which provide information much more relevant than any primary sequence could. Applicants submit that the specification provides specific structural features as identifying characteristics. Essentially the entire specification deals with defining these identifying characteristics. While, as the Office notes on page 9 of the Office Action, there might be no "specific DNA motif" in the sense that there is no overall primary sequence motif (apart from certain binding sites), there is an array of structural motifs, all of which are defined in detail in the specification.

Thus, in the context of a DNA structure whose function is not necessarily correlated to its primary sequence, the person skilled in the art would look for characteristics described in the specification to determine possession of the invention. Having laid out the variables involved and the way to adjust them, the specification provides distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (MPEP 2163) (*emphasis added*).

With the disclosure provided by applicants, in particular with the identifying characteristics provided, the species disclosed (3 out of a subgroup of 85 on chromosome 1 and 1 out of a subgroup of 170 on chromosome X) in the specification are of sufficient variety to reflect the variation within the genus to meet the standards set by the written description requirement.

In view of the above arguments demonstrating applicants' possession of the invention in

conformance with the written description requirement, applicants request reconsideration and withdrawal of the rejection of claims 65-91, 101-104 and 112-115 under 37 CFR 112, first paragraph.

35 USC 102 REJECTION

On page 14, the Office continued to reject claim 106 (and cancelled claim 121) under 35 USC 102(b) as allegedly anticipated by **Klehr et al.** (see IDS), which is said to disclose synthetic MAR comprising human β-interferon domain MAR comprising linkers such as EcoRI and Bam HI. The specification is said to not describe what constitutes a variant of SEQ ID NO:25, leading the Office to conclude that the MAR sequence disclosed in Klehr et al. meets this limitation of a variant.

Applicants have previously directed the Office to the definition of "variant" in the specification. The Office rejected this argument by stating that the type of substitution and the frequency is undetermined. In response, applicants have further amended the claim to specify further characteristics of the claimed sequence limiting the range of variants considerably and clarifying the type and frequency of substitution. As a result, the human β-interferon domain MAR of Klehr et al. falls not within the scope of the amended claim 106.

35 USC 103 REJECTION

On page 14, the Office continued to reject claim 107 under 35 USC 103(a) as obvious over Klehr et al. expressing the opinion that it would have been obvious to add a BglII – BamHI linkers to a synthetic MAR sequence based on the choice of appropriate multiple cloning sites on the vector.

Claim 107 depends from claim 106, which applicants have amended as discussed above to more clearly distinguish over Klehr et al. As Klehr et al. does not teach the subject matter of claim 106, the basis of this obviousness rejection has been removed and the claim should be allowable.

Conclusion

For the reasons discussed above, applicants submit that all pending claims are in condition for allowance. Applicants respectfully request the withdrawal of all objections and rejections, and to allow this application to issue.

The Office is urged to call the undersigned at the number provided below, to address any outstanding issues.

The Commissioner is authorized to charge fee deficiencies and overpayment in connection with this filing to undersign's deposit account 50-3135.

Respectfully submitted,
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